```
                GCTATAAGGA TCACGCGCCC CAGTCGACGC TGAGCTCCTC TGCTACTCAG AGTTGCAACC TCAGCCTCGCT

ATG GCT CCC AGC AGC CCC CGG CCC GCG CTG CCC GCA CTC CTG GTC CTG CTC GGG GCT CTG TTC CCA
MET ALA PRO SER SER PRO ARG PRO ALA LEU PRO ALA LEU LEU VAL LEU LEU GLY ALA LEU PHE PRO

GGA CCT GGC AAT GCC CAG ACA TCT GTG TCC CCC TCA AAA GTC ATC CTG CCC CGG GGA GGC TCC GTG
GLY PRO GLY ASN ALA GLN THR SER VAL SER PRO SER LYS VAL ILE LEU PRO ARG GLY GLY SER VAL

CTG GTG ACA TGC AGC ACC TCC TGT GAC CAG CCC AAG TTG TTG GGC ATA GAG ACC CCG TTG CCT AAA
LEU VAL THR CYS SER THR SER CYS ASP GLN PRO LYS LEU LEU GLY ILE GLU THR PRO LEU PRO LYS

AAG GAG TTG CTC CTG CCT GGG AAC AAC CGG AAG GTG TAT GAA CTG AGC AAT GTG CAA GAA GAT AGC
LYS GLU LEU LEU LEU PRO GLY ASN ASN ARG LYS VAL TYR GLU LEU SER ASN VAL GLN GLU ASP SER

CAA CCA ATG TGC TAT TCA AAC TGC CCT GAT GGG CAG TCA ACA GCT AAA ACC TTC CTC ACC GTG TAC
GLN PRO MET CYS TYR SER ASN CYS PRO ASP GLY GLN SER THR ALA LYS THR PHE LEU THR VAL TYR

TGG ACT CCA GAA CGG GTG GAA CTG GCA CCC CTC CCC TCT TGG CAG CCA GTG GGC AAG AAC CTT ACC
TRP THR PRO GLU ARG VAL GLU LEU ALA PRO LEU PRO SER TRP GLN PRO VAL GLY LYS ASN LEU THR

CTA CGC TGC CAG GTG GAG GGT GGG GCA CCC CGG GCC AAC CTC ACC GTG GTG CTG CTC CGT GGG GAG
LEU ARG CYS GLN VAL GLU GLY GLY ALA PRO ARG ALA ASN LEU THR VAL VAL LEU LEU ARG GLY GLU

AAG GAG CTG AAA CGG GAG CCA GCT GTG GGG GAG CCC GCT GAG GTC ACG ACC ACG GTG CTG GTG AGG
LYS GLU LEU LYS ARG GLU PRO ALA VAL GLY GLU PRO ALA GLU VAL THR THR THR VAL LEU VAL ARG

AGA GAT CAC CAT GGA GCC AAT TTC TCG TGC CGC ACT GAA CTG GAC CTG CGG CCC CAA GGG CTG GAG
ARG ASP HIS HIS GLY ALA ASN PHE SER CYS ARG THR GLU LEU ASP LEU ARG PRO GLN GLY LEU GLU
```

FIG. 1A

```
CTG TTT GAG AAC ACC TCG GCC CCC TAC CAG CTC CAG ACC TTT GTC CTG CCA GCG ACT CCC CCA CAA
LEU PHE GLU ASN THR SER ALA PRO TYR GLN LEU GLN THR PHE VAL LEU PRO ALA THR PRO PRO GLN

CTT GTC AGC CCC CGG GTC CTA GAG GTG GAC ACG CAG GGG ACC GTG GTC TGT TCC CTG GAC GGG CTG
LEU VAL SER PRO ARG VAL LEU GLU VAL ASP THR GLN GLY THR VAL VAL CYS SER LEU ASP GLY LEU

TTC CCA GTC TCG GAG GCC CAG GTC CAC CTG GCA CTG GGG GAC CAG AGG TTG AAC CCC ACA GTC ACC
PHE PRO VAL SER GLU ALA GLN VAL HIS LEU ALA LEU GLY ASP GLN ARG LEU ASN PRO THR VAL THR

TAT GGC AAC GAC TCC TTC TCG GCC AAG GCC TCA GTC AGT GTG ACC GCA GAG GAC GAG GGC ACC CAG
TYR GLY ASN ASP SER PHE SER ALA LYS ALA SER VAL SER VAL THR ALA GLU ASP GLU GLY THR GLN

CGG CTG ACG TGT GCA GTA ATA CTG GGG AAC CAG AGC CAG GAG ACA CTG CAG ACA GTG ACC ATC TAC
ARG LEU THR CYS ALA VAL ILE LEU GLY ASN GLN SER GLN GLU THR LEU GLN THR VAL THR ILE TYR

AGC TTT CCG GCG CCC AAC GTG ATT CTG ACG AAG CCA GAG GTC TCA GAA GGG ACC GAG GTG ACA GTG
SER PHE PRO ALA PRO ASN VAL ILE LEU THR LYS PRO GLU VAL SER GLU GLY THR GLU VAL THR VAL

AAG TGT GAG GCC CAC CCT AGA GCC AAG GTG ACG CTG AAT GGG GTT CCA GCC CAG CCA CTG GGC CCG
LYS CYS GLU ALA HIS PRO ARG ALA LYS VAL THR LEU ASN GLY VAL PRO ALA GLN PRO LEU GLY PRO

AGG GCC CAG CTC CTG CTG AAG GCC ACC CCA GAG GAC AAC GGG CGC AGC TTC TCC TGC TCT GCA ACC
ARG ALA GLN LEU LEU LEU LYS ALA THR PRO GLU ASP ASN GLY ARG SER PHE SER CYS SER ALA THR

CTG GAG GTG GCC GGC CAG CTT ATA CAC AAG AAC CAG ACC CGG GAG CTT CGT GTC CTG TAT GGC CCC
LEU GLU VAL ALA GLY GLN LEU ILE HIS LYS ASN GLN THR ARG GLU LEU ARG VAL LEU TYR GLY PRO

CGA CTG GAC GAG AGG GAT TGT CCG GGA AAC TGG ACG TGG CCA GAA AAT TCC CAG CAG ACT CCA ATG
ARG LEU ASP GLU ARG ASP CYS PRO GLY ASN TRP THR TRP PRO GLU ASN SER GLN GLN THR PRO MET

TGC CAG GCT TGG GGG AAC CCA TTG CCC GAG CTC AAG TGT CTA AAG GAT GGC ACT TTC CCA CTG CCC
CYS GLN ALA TRP GLY ASN PRO LEU PRO GLU LEU LYS CYS LEU LYS ASP GLY THR PHE PRO LEU PRO
```

FIG. 1B

```
ATC GGG GAA TCA GTG ACT GTC ACT CGA GAT CTT GAG GGC ACC TAC CTC TGT CGG GCC AGG AGC ACT
ILE GLY GLU SER VAL THR VAL THR ARG ASP LEU GLU GLY THR TYR LEU CYS ARG ALA ARG SER THR

CAA GGG GAG GTC ACC CGC GAG GTG ACC GTG AAT GTG CTC TCC CCC CGG TAT GAG ATT GTC ATC ATC
GLN GLY GLU VAL THR ARG GLU VAL THR VAL ASN VAL LEU SER PRO ARG TYR GLU ILE VAL ILE ILE

ACT GTG GTA GCA GCC GCA GTC ATA ATG GGC ACT GCA GGC CTC AGC ACG TAC CTC TAT AAC CGC CAG
THR VAL VAL ALA ALA ALA VAL ILE MET GLY THR ALA GLY LEU SER THR TYR LEU TYR ASN ARG GLN

CGG AAG ATC AAG AAA TAC AGA CTA CAA CAG GCC CAA AAA GGG ACC CCC ATG AAA CCG AAC ACA CAA
ARG LYS ILE LYS LYS TYR ARG LEU GLN GLN ALA GLN LYS GLY THR PRO MET LYS PRO ASN THR GLN

GCC ACG CCT CCC TGA ACCTATCCCG GGACAGGGCC TCTTCCTCGG CCTTCCCATA TTGGTGGCAG TGGTGCCACA
ALA THR PRO PRO ***

CTGAACAGAG TGGAAGACAT ATGCCATGCA GCTACACCTA CCGGCCCTGG GACGCCGGAG GACAGGGCAT TGTCCTCAGT

CAGATACAAC AGCATTTGGG GCCATGGTAC CTGCACACCT AAAACACTAG GCCACGCATC TGATCTGTAG TCACATGACT

AAGCCAAGAG GAAGGAGCAA GACTCAAGAC ATGATTGATG GATGTTAAAG TCTAGCCTGA TGAGAGGGGA AGTGGTGGGG

GAGACATAGC CCCACCATGA GGACATACAA CTGGGAAATA CTGAAACTTG CTGCCTATTG GGTATGCTGA GGCCCACAGA

CTTACAGAAG AAGTGGCCCT CCATAGACAT GTGTAGCATC AAAACACAAA GGCCCACACT TCCTGACGGA TGCCAGCTTG

GGCACTGCTG TCTACTGACC CCAACCCTTG ATGATATGTA TTTATTCATT TGTTATTTTA CCAGCTATTT ATTGAGTGTC

TTTTATGTAG GCTAAATGAA CATAGGTCTC TGGCCTCACG GAGCTCCCAG TCCATGTCAC ATTCAAGGTC ACCAGGTACA

GTTGTACAGG TTGTACACTG CAGGAGAGTG CCTGGCAAAA AGATCAAATG GGGCTGGGAC TTCTCATTGG CCAACCTGCC

TTTCCCCAGA AGGAGTGATT TTTCTATCGG CACAAAAGCA CTATATGGAC TGGTAATGGT TCACAGGTTC AGAGATTACC
```

FIG. 1C

CAGTGAGGCC TTATTCCTCC CTTCCCCCCA AAACTGACAC CTTTGTTAGC CACCTCCCCA CCCACATACA TTTCTGCCAG
TGTTACAATG ACACTCAGCG GTCATGTCTG GACATGAGTG CCCAGGGAAT ATGCCCAAGC TATGCCTTGT CCTCTTGTCC
TGTTTGCATT TCACTGGGAG CTTGCACTAT TGCAGCTCCA GTTTCCTGCA GTGATCAGGG TCCTGCAAGC AGTGGGGAAG
GGGGCCAAGG TATTGGAGGA CTCCCTCCCA GCTTTGGAAG GGTCATCCGC GTGTGTGTGT GTGTGTATGT GTAGACAAGC
TCTCGCTCTG TCACCCAGGC TGGAGTGCAG TGGTGCAATC ATGGTTCACT GCAGTCTTGA CCTTTTGGGC TCAAGTGATC
CTCCCACCTC AGCCTCCTGA GTAGCTGGGA CCATAGGCTC ACAACACCAC ACCTGGCAAA TTTGATTTTT TTTTTTTTTT
TCAGAGACGG GGTCTCGCAA CATTGCCCAG ACTTCCTTTG TGTTAGTTAA TAAAGCTTTC TCAACTGCCA AAAAAAAAAA
AAAAAAA

FIG. 1D

FIG. 2A

```
TTCACATCAA AACTCCTATA CTGACCTGAG ACAGAGGCAG CAGTGATACC CACCTGAGAG ATCCTGTGTT TGA

ACAACTG CTTCCCAAAA CGGAAAGTAT TTCAAGCCTA AACCTTTGGG TGAAAAGAAC TCTTGAAGTC ATG ATT
                                                                          met ile

GCT TCA CAG TTT CTC TCA GCT CTC ACT TTG GTG CTT CTC ATT AAA GAG AGT GGA GCC TGG
ala ser gln phe leu ser ala leu thr leu val leu leu ile lys glu ser gly ala trp

TCT TAC AAC ACC TCC ACG GAA GCT ATG ACT TAT GAT GAG GCC AGT GCT TAT TGT CAG CAA
ser tyr asn thr ser thr glu ala met thr tyr asp glu ala ser ala tyr cys gln gln

AGG TAC ACA CAC CTG GTT GCA ATT CAA AAC AAA GAA GAG ATT GAG TAC CTA AAC TCC ATA
arg tyr thr his leu val ala ile gln asn lys glu glu ile glu tyr leu asn ser ile

TTG AGC TAT TCA CCA AGT TAT TAC TGG ATT GGA ATC AGA AAA GTC AAC AAT GTG TGG GTC
leu ser tyr ser pro ser tyr tyr trp ile gly ile arg lys val asn asn val trp val

TGG GTA GGA ACC CAG AAA CCT CTG ACA GAA GAA GCC AAG AAC TGG GCT CCA GGT GAA CCC
trp val gly thr gln lys pro leu thr glu glu ala lys asn trp ala pro gly glu pro

AAC AAT AGG CAA AAA GAT GAG GAC TGC GTG GAG ATC TAC ATC AAG AGA GAA AAA GAT GTG
asn asn arg gln lys asp glu asp cys val glu ile tyr ile lys arg glu lys asp val

GGC ATG TGG AAT GAT GAG AGG TGC AGC AAG AAG AAG CTT GCC CTA TGC TAC ACA GCT GCC
gly met trp asn asp glu arg cys ser lys lys lys leu ala leu cys tyr thr ala ala

TGT ACC AAT ACA TCC TGC AGT GGC CAC GGT GAA TGT GTA GAG ACC ATC AAT AAT TAC ACT
cys thr asn thr ser cys ser gly his gly glu cys val glu thr ile asn asn tyr thr

TGC AAG TGT GAC CCT GGC TTC AGT GGA CTC AAG TGT GAG CAA ATT GTG AAC TGT ACA GCC
cys lys cys asp pro gly phe ser gly leu lys cys glu gln ile val asn cys thr ala
```

```
CTG GAA TCC CCT GAG CAT GGA AGC CTG GTT TGC AGT CAC CCA CTG GGA AAC TTC AGC TAC
leu glu ser pro glu his gly ser leu val cys ser his pro leu gly asn phe ser tyr

AAT TCT TCC TGC TCT ATC AGC TGT GAT AGG GGT TAC CTG CCA AGC AGC ATG GAG ACC ATG
asn ser ser cys ser ile ser cys asp arg gly tyr leu pro ser ser met glu thr met

CAG TGT ATG TCC TCT GGA GAA TGG AGT GCT CCT ATT CCA GCC TGC AAT GTG GTT GAG TGT
gln cys met ser ser gly glu trp ser ala pro ile pro ala cys asn val val glu cys

GAT GCT GTG ACA AAT CCA GCC AAT GGG TTC GTG GAA TGT TTC CAA AAC CCT GGA AGC TTC
asp ala val thr asn pro ala asn gly phe val glu cys phe gln asn pro gly ser phe

CCA TGG AAC ACA ACC TGT ACA TTT GAC TGT GAA GAA GGA TTT GAA CTA ATG GGA GCC CAG
pro trp asn thr thr cys thr phe asp cys glu glu gly phe glu leu met gly ala gln

AGC CTT CAG TGT ACC TCA TCT GGG AAT TGG GAC AAC GAG AAG CCA ACG TGT AAA GCT GTG
ser leu gln cys thr ser ser gly asn trp asp asn glu lys pro thr cys lys ala val

ACA TGC AGG GCC GTC CGC CAG CCT CAG AAT GGC TCT GTG AGG TGC AGC CAT TCC CCT GCT
thr cys arg ala val arg gln pro gln asn gly ser val arg cys ser his ser pro ala

GGA GAG TTC ACC TTC AAA TCA TCC TGC AAC TTC ACC TGT GAG GAA GGC TTC ATG TTG CAG
gly glu phe thr phe lys ser ser cys asn phe thr cys glu glu gly phe met leu gln

GGA CCA GCC CAG GTT GAA TGC ACC ACT CAA GGG CAG TGG ACA CAG CAA ATC CCA GTT TGT
gly pro ala gln val glu cys thr thr gln gly gln trp thr gln gln ile pro val cys

GAA GCT TTC CAG TGC ACA GCC TTG TCC AAC CCC GAG CGA GGC TAC ATG AAT TGT CTT CCT
glu ala phe gln cys thr ala leu ser asn pro glu arg gly tyr met asn cys leu pro
```

FIG. 2B

```
AGT GCT TCT GGC AGT TTC CGT TAT GGG TCC AGC TGT GAG TTC TCC TGT GAG CAG GGT TTT
ser ala ser gly ser phe arg tyr gly ser ser cys glu phe ser cys glu gln gly phe

GTG TTG AAG GGA TCC AAA AGG CTC CAA TGT GGC CCC ACA GGG GAG TGG GAC AAC GAG AAG
val leu lys gly ser lys arg leu gln cys gly pro thr gly glu trp asp asn glu lys

CCC ACA TGT GAA GCT GTG AGA TGC GAT GCT GTC CAC CAG CCC CCG AAG GGT TTG GTG AGG
pro thr cys glu ala val arg cys asp ala val his gln pro pro lys gly leu val arg

TGT GCT CAT TCC CCT ATT GGA GAA TTC ACC TAC AAG TCC TCT TGT GCC TTC AGC TGT GAG
cys ala his ser pro ile gly glu phe thr tyr lys ser ser cys ala phe ser cys glu

GAG GGA TTT GAA TTA TAT GGA TCA ACT CAA CTT GAG TGC ACA TCT CAG GGA CAA TGG ACA
glu gly phe glu leu tyr gly ser thr gln leu glu cys thr ser gln gly gln trp thr

GAA GAG GTT CCT TCC TGC CAA GTG GTA AAA TGT TCA AGC CTG GCA GTT CCG GGA AAG ATC
glu glu val pro ser cys gln val val lys cys ser ser leu ala val pro gly lys ile

AAC ATG AGC TGC AGT GGG GAG CCC GTG TTT GGC ACT GTG TGC AAG TTC GCC TGT CCT GAA
asn met ser cys ser gly glu pro val phe gly thr val cys lys phe ala cys pro glu

GGA TGG ACG CTC AAT GGC TCT GCA GCT CGG ACA TGT GGA GCC ACA GGA CAC TGG TCT GGC
gly trp thr leu asn gly ser ala ala arg thr cys gly ala thr gly his trp ser gly

CTG CTA CCT ACC TGT GAA GCT CCC ACT GAG TCC AAC ATT CCC TTG GTA GCT GGA CTT TCT
leu leu pro thr cys glu ala pro thr glu ser asn ile pro leu val ala gly leu ser

GCT GCT GGA CTC TCC CTC CTG ACA TTA GCA CCA TTT CTC CTC TGG CTT CGG AAA TGC TTA
ala ala gly leu ser leu leu thr leu ala pro phe leu leu trp leu arg lys cys leu

CGG AAA GCA AAG AAA TTT GTT CCT GCC AGC AGC TGC CAA AGC CTT GAA TCA GAC GGA AGC
arg lys ala lys lys phe val pro ala ser ser cys gln ser leu glu ser asp gly ser
```

FIG. 2C

TAC CAA AAG CCT TCT TAC ATC CTT TAA GTTCAAA AGAATCAGAA ACAGGTGCAT CTGGGGAACT A
tyr gln lys pro ser tyr ile leu ***

GAGGGATAC ACTGAAGTTA ACAGAGACAG ATAACTCTCC TCGGGTCTCT GGCCCTTCTT GCCTACTATG CCAG

ATGCCT TTATGGCTGA AACCGCAACA CCCATCACCA CTTCAATAGA TCAAAGTCCA GCAGGCAAGG ACGGCCT

TCA ACTGAAAAGA CTCAGTGTTC CCTTTCCTAC TCTCAGGATC AAGAAAGTGT TGGCTAATGA AGGGAAAGGA

TATTTTCTTC CAAGCAAAGG TGAAGAGACC AAGACTCTGA AATCTCAGAA TTCCTTTTCT AACTCTCCCT TG

CTCGCTGT AAAATCTTGG CACAGAAACA CAATATTTTG TGGCTTTCTT TCTTTTGCCC TTCACAGTGT TTCGA

CAGCT GATTACACAG TTGCTGTCAT AAGAATGAAT AATAATTATC CAGAGTTTAG AGGAAAAAAA TGACTAAA

AA TATTATAACT TAAAAAAATG ACAGATGTTG AATGCCCACA GGCAAATGCA TGGAGGGTTG TTAATGGTGC

AAATCCTACT GAATGCTCTG TGCGAGGGTT ACTATGCACA ATTTAATCAC TTTCATCCCT ATGGGATTCA GTG

CTTCTTA AAGAGTTCTT AAGGATTGTG ATATTTTTAC TTGCATTGAA TATATTATAA TCTTCCATAC TTCTTC

ATTC AATACAAGTG TGGTAGGGAC TTAAAAAACT TGTAAATGCT GTCAACTATG ATATGGTAAA AGTTACTTA

T TCTAGATTAC CCCCTCATTG TTTATTAACA AATTATGTTA CATCTGTTTT AAATTTATTT CAAAAAGGGA A

ACTATTGTC CCCTAGCAAG GCATGATGTT AACCAGAATA AAGTTCTGAG TGTTTTTACT ACAGTTGTTT TTTG

AAAACA TGGTAGAATT GGAGAGTAAA AACTGAATGG AAGGTTTGTA TATTGTCAGA TATTTTTTCA GAAATAT

GTG GTTTCCACGA TGAAAAACTT CCATGAGGCC AAACGTTTTG AACTAATAAA AGCATAAATG CAAACACACA

AAGGTATAAT TTTATGAATG TCTTTGTTGG AAAAGAATAC AGAAAGATGG ATGTGCTTTG CATTCCTACA AA

GATGTTTG TCAGATGTGA TATGTAAACA TAATTCTTGT ATATTATGGA AGATTTTAAA TTCACAATAG AAACT

FIG. 2D

CACCA TGTAAAAGAG TCATCTGGTA GATTTTTAAC GAATGAAGAT GTCTAATAGT TATTCCCTAT TTGTTTTC
TT CTGTATGTTA GGGTGCTCTG GAAGAGAGGA ATGCCTGTGT GAGCAAGCAT TTATGTTTAT TTATAAGCAG
ATTTAACAAT TCCAAAGGAA TCTCCAGTTT TCAGTTGATC ACTGGCAATG AAAAATTCTC AGTCAGTAAT TGC
CAAAGCT GCTCTAGCCT TGAGGAGTGT GAGAATCAAA ACTCTCCTAC ACTTCCATTA ACTTAGCATG TGTTGA
AAAA AAAAGTTTCA GAGAAGTTCT GGCTGAACAC TGGCAACGAC AAAGCCAACA GTCAAAACAG AGATGTGAT
A AGGATCAGAA CAGCAGAGGT TCTTTTAAAG GGGCAGAAAA ACTCTGGGAA ATAAGAGAGA ACAACTACTG T
GATCAGGCT ATGTATGGAA TACAGTGTTA TTTTCTTTGA AATTGTTTAA GTGTTGTAAA TATTTATGTA AACT
GCATTA GAAATTAGCT GTGTGAAATA CCAGTGTGGT TTGTGTTTGA GTTTTATTGA GAATTTTAAA TTATAAC
TTA AAATATTTTA TAATTTTTAA AGTATATATT TATTTAAGCT TATGTCAGAC CTATTTGACA TAACACTATA
AAGGTTGACA ATAAATGTGC TTATGTTT

FIG. 2E

FIG. 3A

```
CGGGCCTCAC TGGCTTCAGG AGCTGAATAC CCTCCCAGGC ACACACAGGT GGGACACAAA TAAGGGTTTT GGA

ACCACTA TTTTCTCATC ACGACAGCAA CTTAAA ATG CCT GGG AAG ATG GTC GTG ATC CTT GGA GCC
                                     met pro gly lys met val val ile leu gly ala

TCA AAT ATA CTT TGG ATA ATG TTT GCA GCT TCT CAA GCT TTT AAA ATC GAG ACC ACC CCA
ser asn ile leu trp ile met phe ala ala ser gln ala phe lys ile glu thr thr pro

GAA TCT AGA TAT CTT GCT CAG ATT GGT GAC TCC GTC TCA TTG ACT TGC AGC ACC ACA GGC
glu ser arg tyr leu ala gln ile gly asp ser val ser leu thr cys ser thr thr gly

TGT GAG TCC CCA TTT TTC TCT TGG AGA ACC CAG ATA GAT AGT CCA CTG AAT GGG AAG GTG
cys glu ser pro phe phe ser trp arg thr gln ile asp ser pro leu asn gly lys val

ACG AAT GAG GGG ACC ACA TCT ACG CTG ACA ATG AAT CCT GTT AGT TTT GGG AAC GAA CAC
thr asn glu gly thr thr ser thr leu thr met asn pro val ser phe gly asn glu his

TCT TAC CTG TGC ACA GCA ACT TGT GAA TCT AGG AAA TTG GAA AAA GGA ATC CAG GTG GAG
ser tyr leu cys thr ala thr cys glu ser arg lys leu glu lys gly ile gln val glu

ATC TAC TCT TTT CCT AAG GAT CCA GAG ATT CAT TTG AGT GGC CCT CTG GAG GCT GGG AAG
ile tyr ser phe pro lys asp pro glu ile his leu ser gly pro leu glu ala gly lys

CCG ATC ACA GTC AAG TGT TCA GTT GCT GAT GTA TAC CCA TTT GAC AGG CTG GAG ATA GAC
pro ile thr val lys cys ser val ala asp val tyr pro phe asp arg leu glu ile asp

TTA CTG AAA GGA GAT CAT CTC ATG AAG AGT CAG GAA TTT CTG GAG GAT GCA GAC AGG AAG
leu leu lys gly asp his leu met lys ser gln glu phe leu glu asp ala asp arg lys

TCC CTG GAA ACC AAG AGT TTG GAA GTA ACC TTT ACT CCT GTC ATT GAG GAT ATT GGA AAA
ser leu glu thr lys ser leu glu val thr phe thr pro val ile glu asp ile gly lys

GTT CTT GTT TGC CGA GCT AAA TTA CAC ATT GAT GAA ATG GAT TCT GTG CCC ACA GTA AGG
val leu val cys arg ala lys leu his ile asp glu met asp ser val pro thr val arg
```

```
CAG GCT GTA AAA GAA TTG CAA GTC TAC ATA TCA CCC AAG AAT ACA GTT ATT TCT GTG AAT
gln ala val lys glu leu gln val tyr ile ser pro lys asn thr val ile ser val asn

CCA TCC ACA AAG CTG CAA GAA GGT GGC TCT GTG ACC ATG ACC TGT TCC AGC GAG GGT CTA
pro ser thr lys leu gln glu gly gly ser val thr met thr cys ser ser glu gly leu

CCA GCT CCA GAG ATT TTC TGG AGT AAG AAA TTA GAT AAT GGG AAT CTA CAG CAC CTT TCT
pro ala pro glu ile phe trp ser lys lys leu asp asn gly asn leu gln his leu ser

GGA AAT GCA ACT CTC ACC TTA ATT GCT ATG AGG ATG GAA GAT TCT GGA ATT TAT GTG TGT
gly asn ala thr leu thr leu ile ala met arg met glu asp ser gly ile tyr val cys

GAA GGA GTT AAT TTG ATT GGG AAA AAC AGA AAA GAG GTG GAA TTA ATT GTT CAA GCA TTC
glu gly val asn leu ile gly lys asn arg lys glu val glu leu ile val gln ala phe

CCT AGA GAT CCA GAA ATC GAG ATG AGT GGT GGC CTC GTG AAT GGG AGC TCT GTC ACT GTA
pro arg asp pro glu ile glu met ser gly gly leu val asn gly ser ser val thr val

AGC TGC AAG GTT CCT AGC GTG TAC CCC CTT GAC CGG CTG GAG ATT GAA TTA CTT AAG GGG
ser cys lys val pro ser val tyr pro leu asp arg leu glu ile glu leu leu lys gly

GAG ACT ATT CTG GAG AAT ATA GAG TTT TTG GAG GAT ACG GAT ATG AAA TCT CTA GAG AAC
glu thr ile leu glu asn ile glu phe leu glu asp thr asp met lys ser leu glu asn

AAA AGT TTG GAA ATG ACC TTC ATC CCT ACC ATT GAA GAT ACT GGA AAA GCT CTT GTT TGT
lys ser leu glu met thr phe ile pro thr ile glu asp thr gly lys ala leu val cys

CAG GCT AAG TTA CAT ATT GAT GAC ATG GAA TTC GAA CCC AAA CAA AGG CAG AGT ACG CAA
gln ala lys leu his ile asp asp met glu phe glu pro lys gln arg gln ser thr gln

ACA CTT TAT GTC AAT GTT GCC CCC AGA GAT ACA ACC GTC TTG GTC AGC CCT TCC TCC ATC
thr leu tyr val asn val ala pro arg asp thr thr val leu val ser pro ser ser ile

CTG GAG GAA GGC AGT TCT GTG AAT ATG ACA TGC TTG AGC CAG GGC TTT CCT GCT CCG AAA
leu glu glu gly ser ser val asn met thr cys leu ser gln gly phe pro ala pro lys
```

FIG. 3B

```
ATC CTG TGG AGC AGG CAG CTC CCT AAC GGG GAG CTA CAG CCT CTT TCT GAG AAT GCA ACT
ile leu trp ser arg gln leu pro asn gly glu leu gln pro leu ser glu asn ala thr

CTC ACC TTA ATT TCT ACA AAA ATG GAA GAT TCT GGG GTT TAT TTA TGT GAA GGA ATT AAC
leu thr leu ile ser thr lys met glu asp ser gly val tyr leu cys glu gly ile asn

CAG GCT GGA AGA AGC AGA AAG GAA GTG GAA TTA ATT ATC CAA GTT ACT CCA AAA GAC ATA
gln ala gly arg ser arg lys glu val glu leu ile ile gln val thr pro lys asp ile

AAA CTT ACA GCT TTT CCT TCT GAG AGT GTC AAA GAA GGA GAC ACT GTC ATC ATC TCT TGT
lys leu thr ala phe pro ser glu ser val lys glu gly asp thr val ile ile ser cys

ACA TGT GGA AAT GTT CCA GAA ACA TGG ATA ATC CTG AAG AAA AAA GCG GAG ACA GGA GAC
thr cys gly asn val pro glu thr trp ile ile leu lys lys lys ala glu thr gly asp

ACA GTA CTA AAA TCT ATA GAT GGC GCC TAT ACC ATC CGA AAG GCC CAG TTG AAG GAT GCG
thr val leu lys ser ile asp gly ala tyr thr ile arg lys ala gln leu lys asp ala

GGA GTA TAT GAA TGT GAA TCT AAA AAC AAA GTT GGC TCA CAA TTA AGA AGT TTA ACA CTT
gly val tyr glu cys glu ser lys asn lys val gly ser gln leu arg ser leu thr leu

GAT GTT CAA GGA AGA GAA AAC AAC AAA GAC TAT TTT TCT CCT GAG CTT CTC GTG CTC TAT
asp val gln gly arg glu asn asn lys asp tyr phe ser pro glu leu leu val leu tyr

TTT GCA TCC TCC TTA ATA ATA CCT GCC ATT GGA ATG ATA ATT TAC TTT GCA AGA AAA GCC
phe ala ser ser leu ile ile pro ala ile gly met ile ile tyr phe ala arg lys ala

AAC ATG AAG GGG TCA TAT AGT CTT GTA GAA GCA CAG AAA TCA AAA GTG TAG CTAATGCTTG
asn met lys gly ser tyr ser leu val glu ala gln lys ser lys val ***

ATATGTTCAA CTGGAGACAC TATTTATCTG TGCAAATCCT TGATACTGCT CATCATTCCT TGAGAAAAAC AAT

GAGCTGA GAGGCAGACT TCCCTGAATG TATTGAACTT GGAAAGAAAT GCCCATCTAT GTCCCTTGCT GTGAGC

AAGA AGTCAAAGTA AAACTTGCTG CCTGAAGAAC AGTAACTGCC ATCAAGATGA GAGAACTGGA GGAGTTCCT

T GATCTGTATA TACAATAACA TAATTTGTAC ATATGTAAAA TAAAATTATG CCATAGCAAG ATTGCTTAAAA
```

FIG. 3C

TAGCAACAC TCTATATTTA GATTGTTAAA ATAACTAGTG TTGCTTGGAC TATTATAATT TAATGCATGT TAGG
AAAATT TCACATTAAT ATTTGCTGAC AGCTGACCTT TGTCATCTTT CTTCTATTTT ATTCCCTTTC ACAAAAT
TTT ATTCCTATAT AGTTTATTGA CAATAATTTC AGGTTTTGTA AAGATGCCGG GTTTTATATT TTTATAGACA
AATAATAAGC AAAGGGAGCA CTGGGTTGAC TTTCAGGTAC TAAATACCTC AACCTATGGT ATAATGGTTG AC
TGGGTTTC TCTGTATAGT ACTGGCATGG TACGGAGATG TTTCACGAAG TTTGTTCATC AGACTCCTGT GCAAC
TTTCC CAATGTGGCC TAAAAATGCA ACTTCTTTTT ATTTTCTTTT GTAAATGTTT AGGTTTTTTT GTATAGTA
AA GTGATAATTT CTGGAATTAA AAA

FIG. 3D

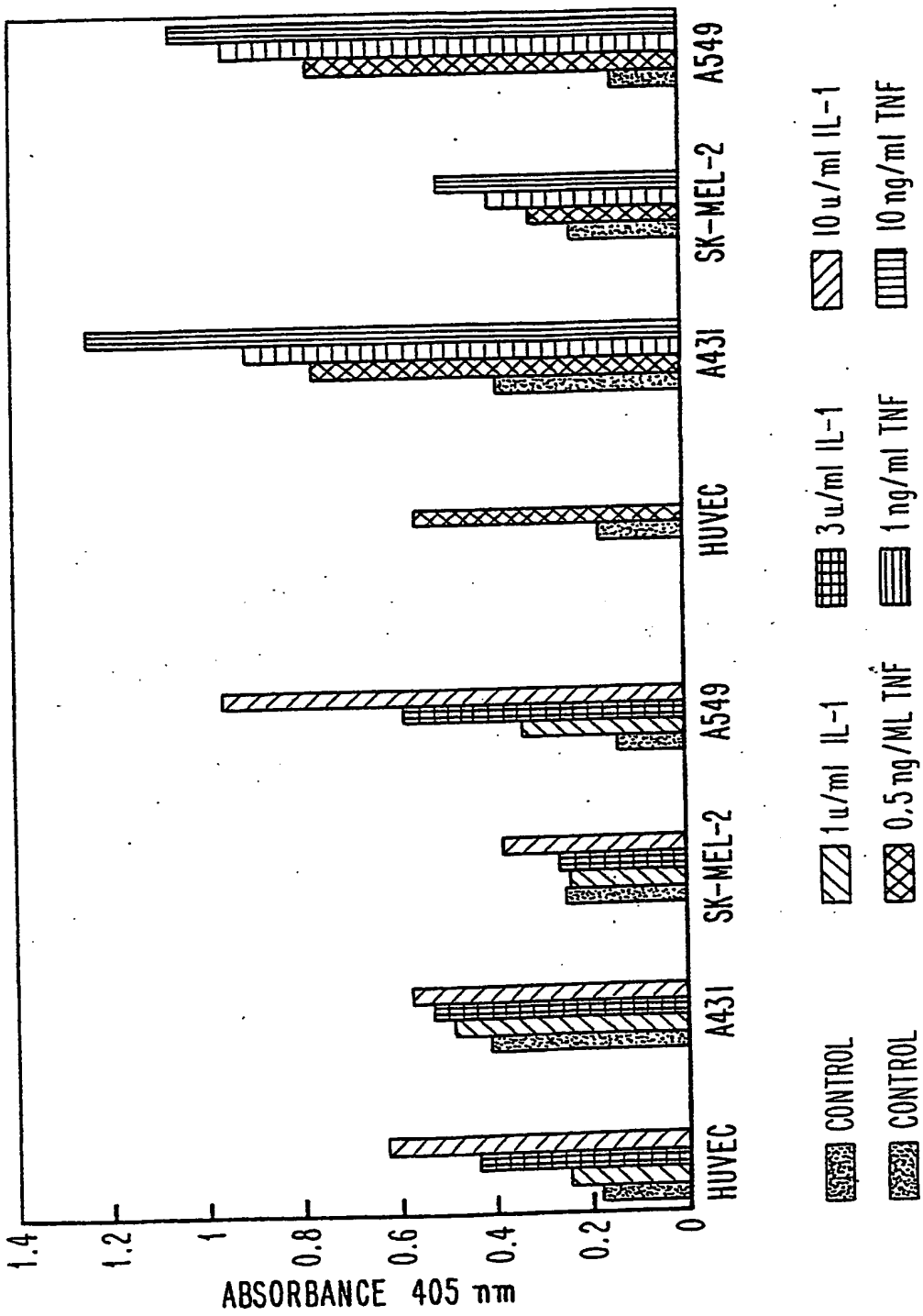
ABSORBANCE 405 nm
0
0.2
0.4
0.6
0.8
1
1.2
1.4
HUVEC
A431
SK-MEL-2
A549
HUVEC
A431
SK-MEL-2
A549
CONTROL
1 u/ml IL-1
3 u/ml IL-1
10 u/ml IL-1
CONTROL
0.5 ng/ML TNF
1 ng/ml TNF
10 ng/ml TNF

FIG. 4

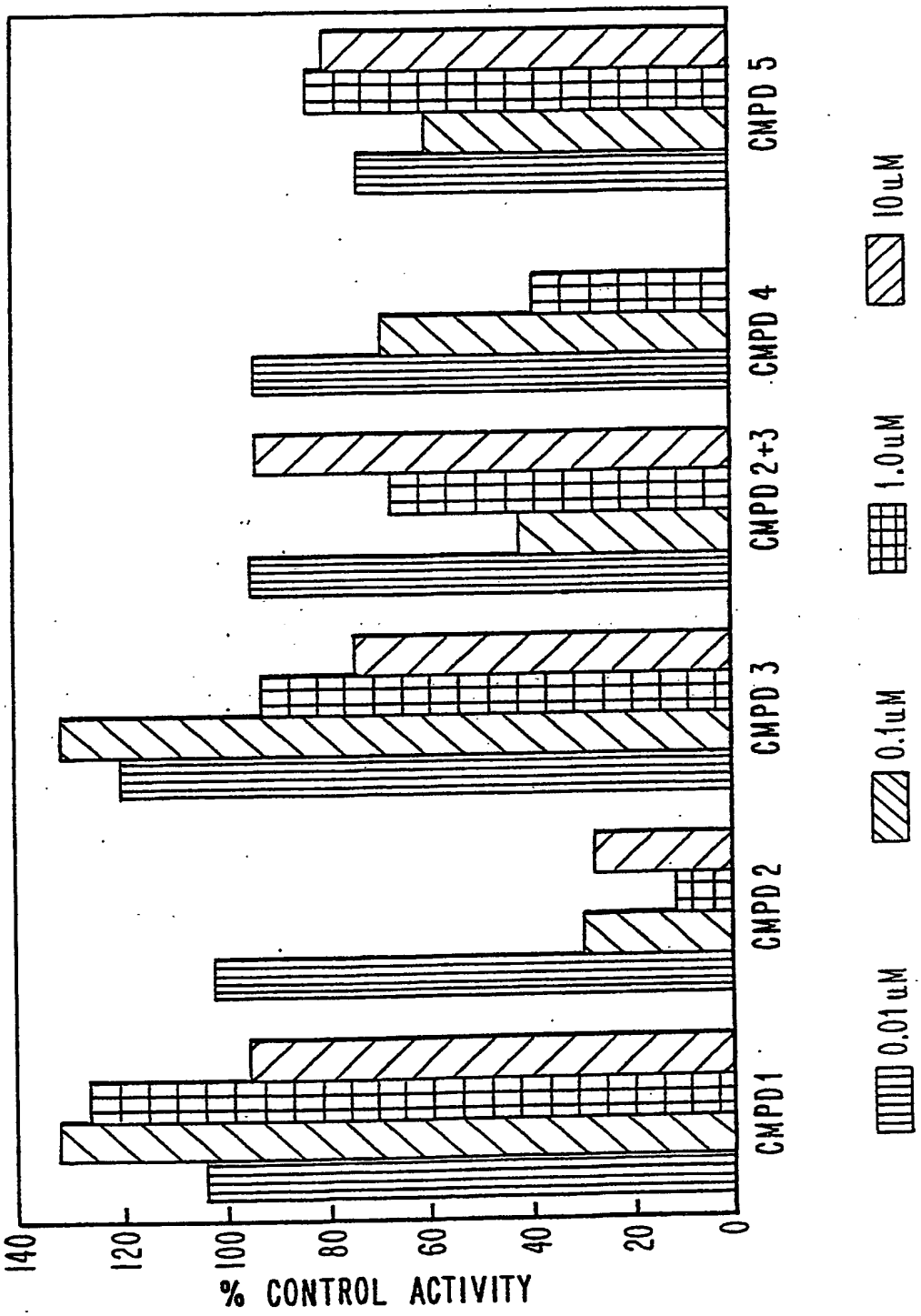
140
120
100
80
60
40
20
0
% CONTROL ACTIVITY
CMPD 1
CMPD 2
CMPD 3
CMPD 2+3
CMPD 4
CMPD 5
0.01uM
0.1uM
1.0uM
10uM

FIG. 5

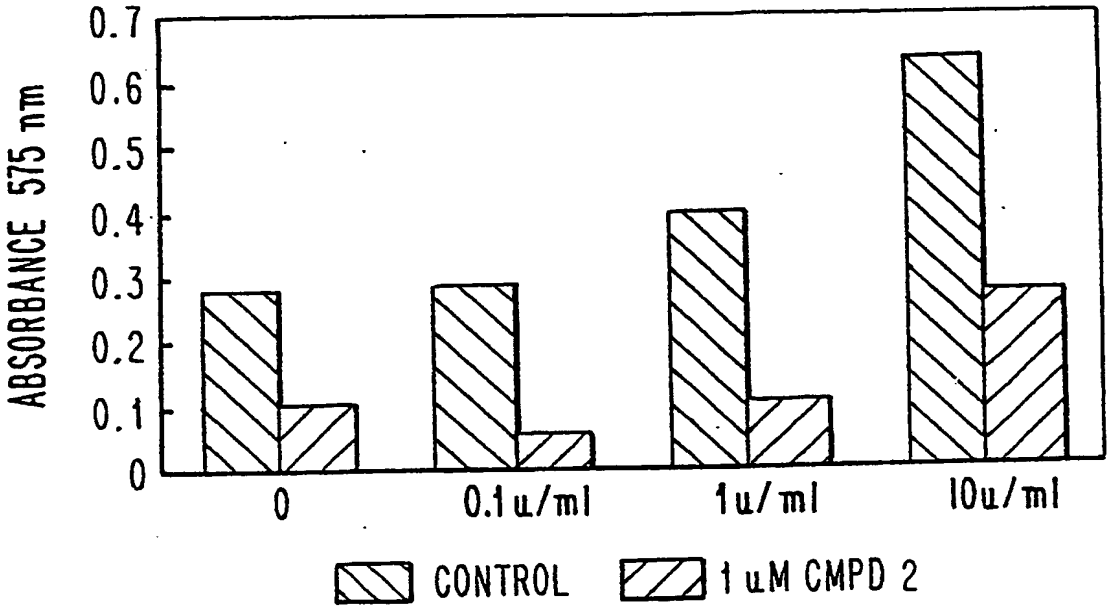
ABSORBANCE 575 nm
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
0.1u/ml
1u/ml
10u/ml
CONTROL
1uM CMPD 2

FIG. 6A

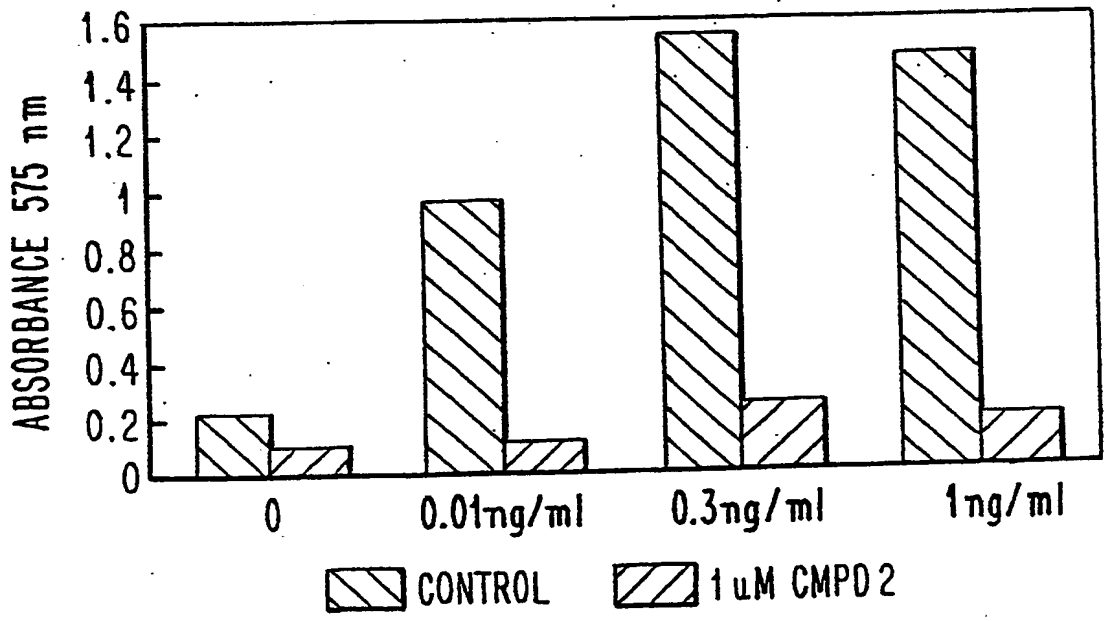
ABSORBANCE 575 nm
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
0
0.01ng/ml
0.3ng/ml
1ng/ml
CONTROL
1uM CMPD 2

FIG. 6B

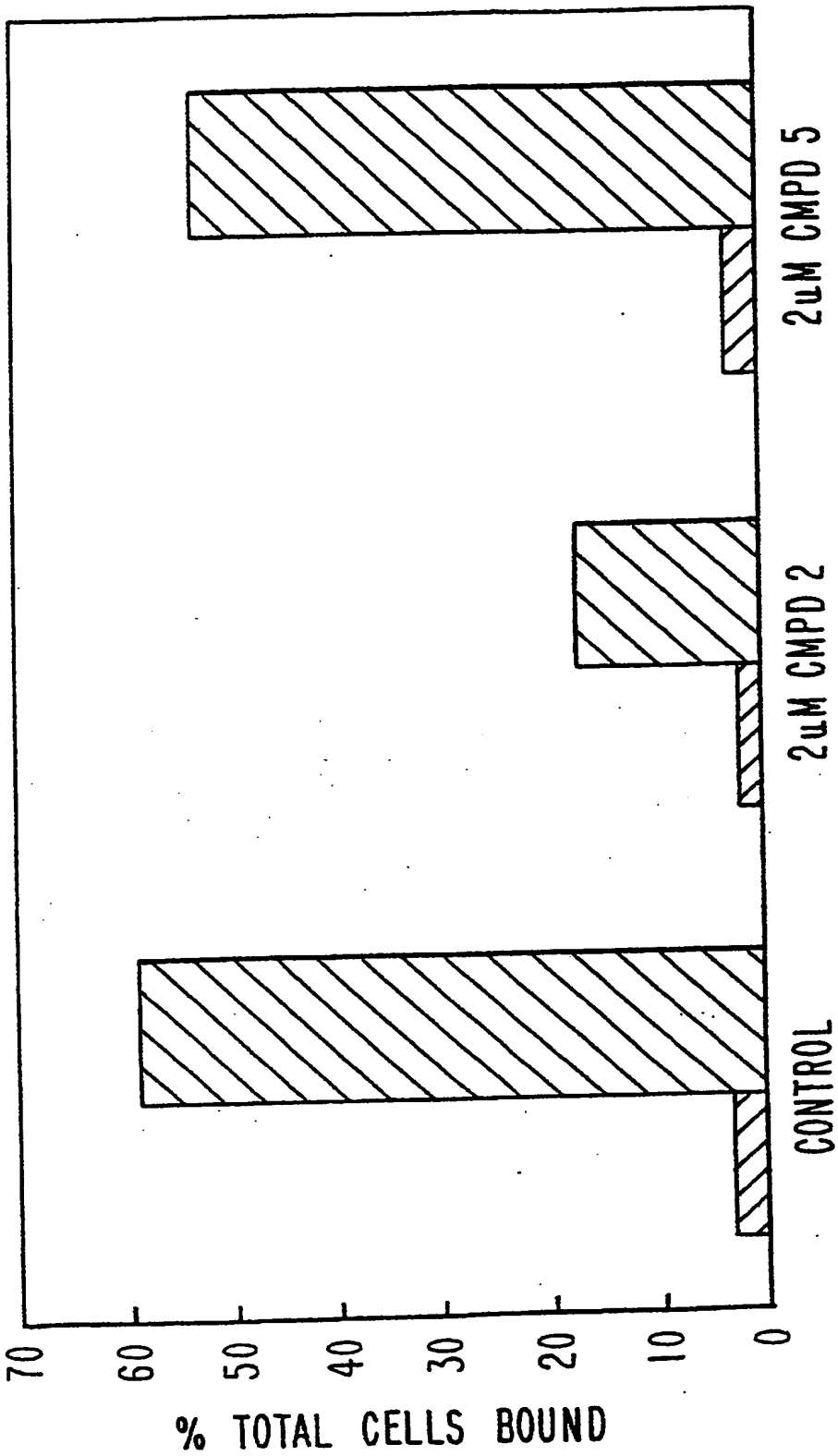
% TOTAL CELLS BOUND
70
60
50
40
30
20
10
0
CONTROL
2uM CMPD 2
2uM CMPD 5
BASAL
1 ng/ml TNF

FIG. 7

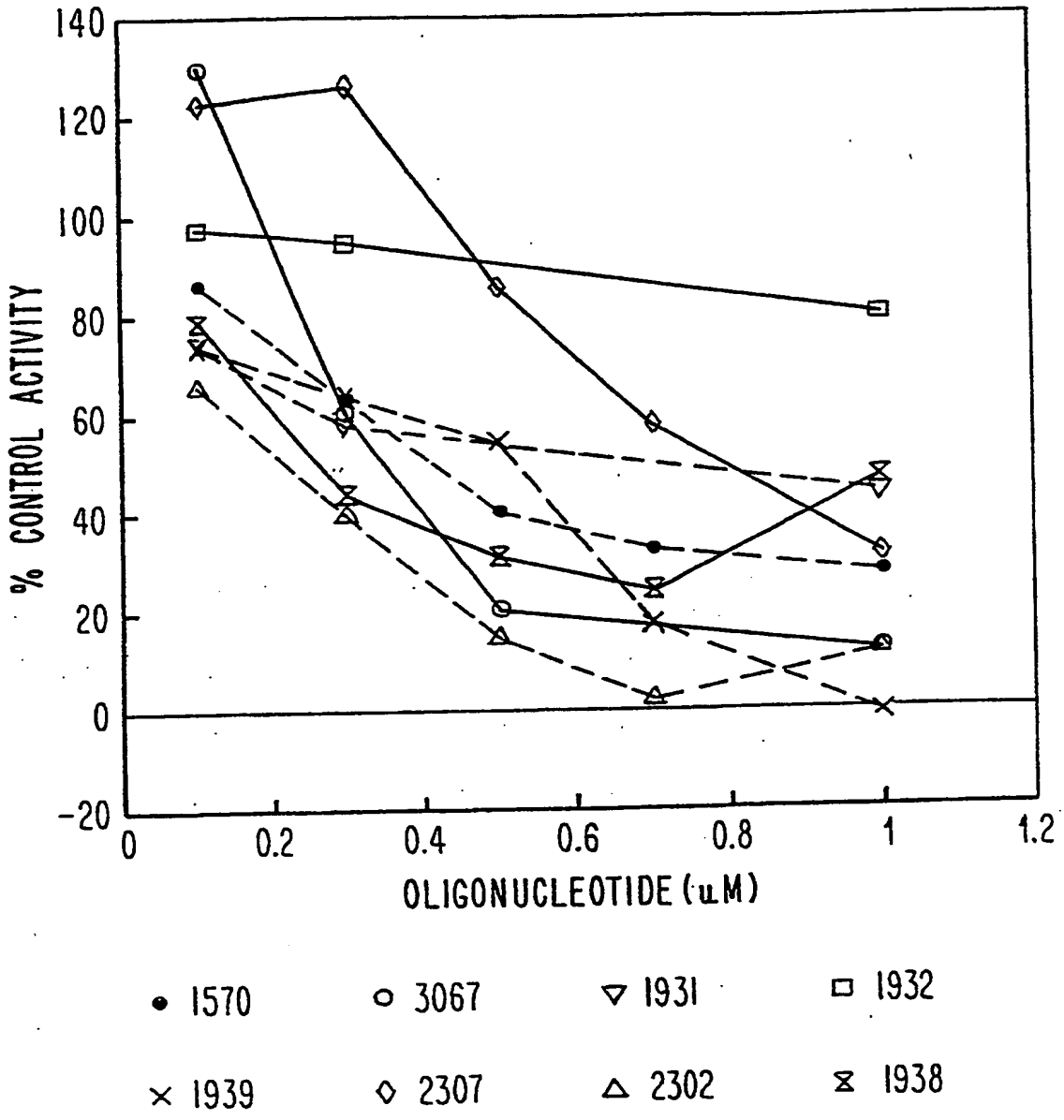
140
120
100
80
60
40
20
0
-20
% CONTROL ACTIVITY
0
0.2
0.4
0.6
0.8
1
1.2
OLIGONUCLEOTIDE (uM)
1570
3067
1931
1932
1939
2307
2302
1938

FIG. 8

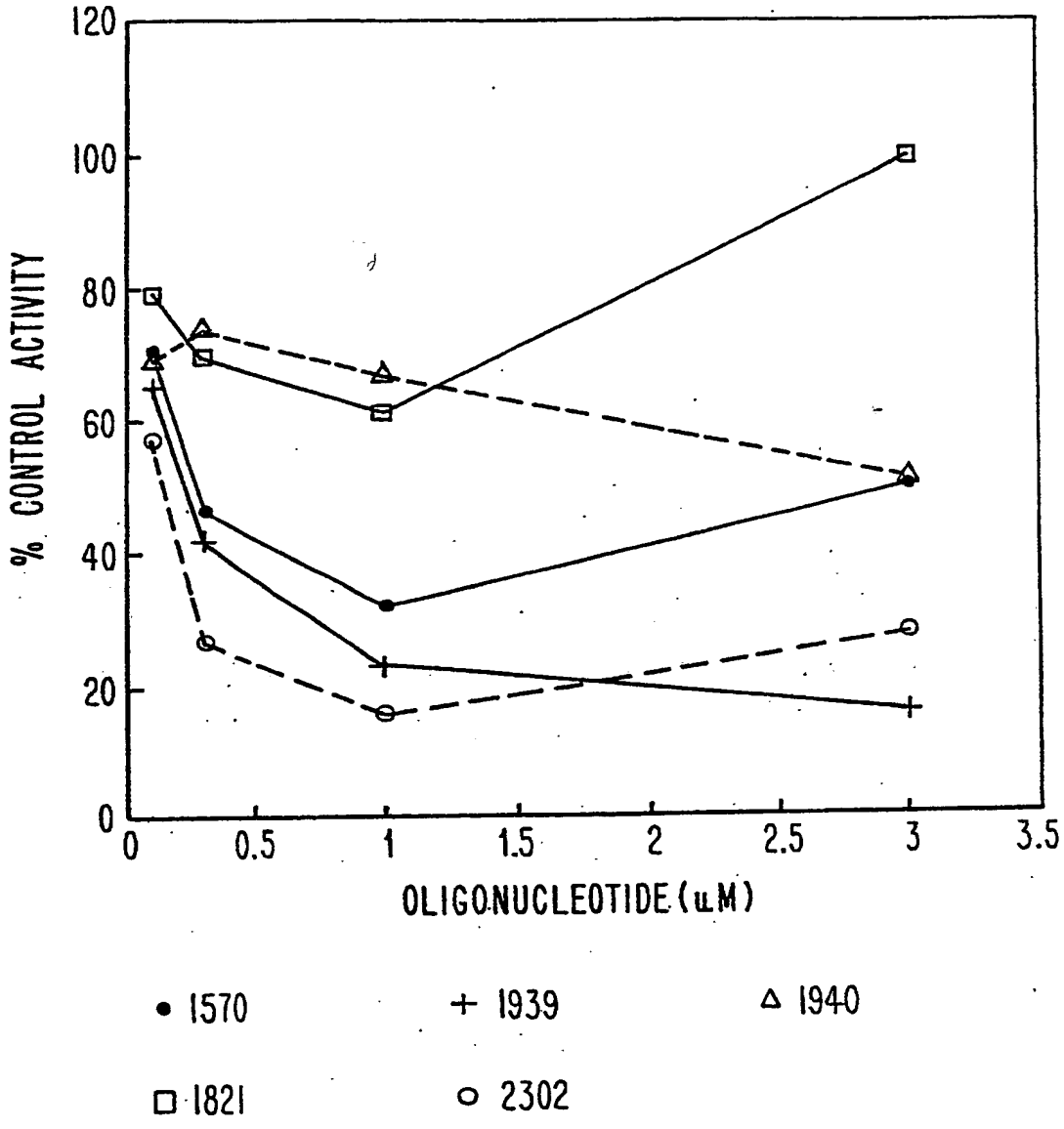
120
100
80
60
40
20
0
% CONTROL ACTIVITY
0
0.5
1
1.5
2
2.5
3
3.5
OLIGONUCLEOTIDE (uM)
• 1570
+ 1939
△ 1940
□ 1821
○ 2302

FIG. 9

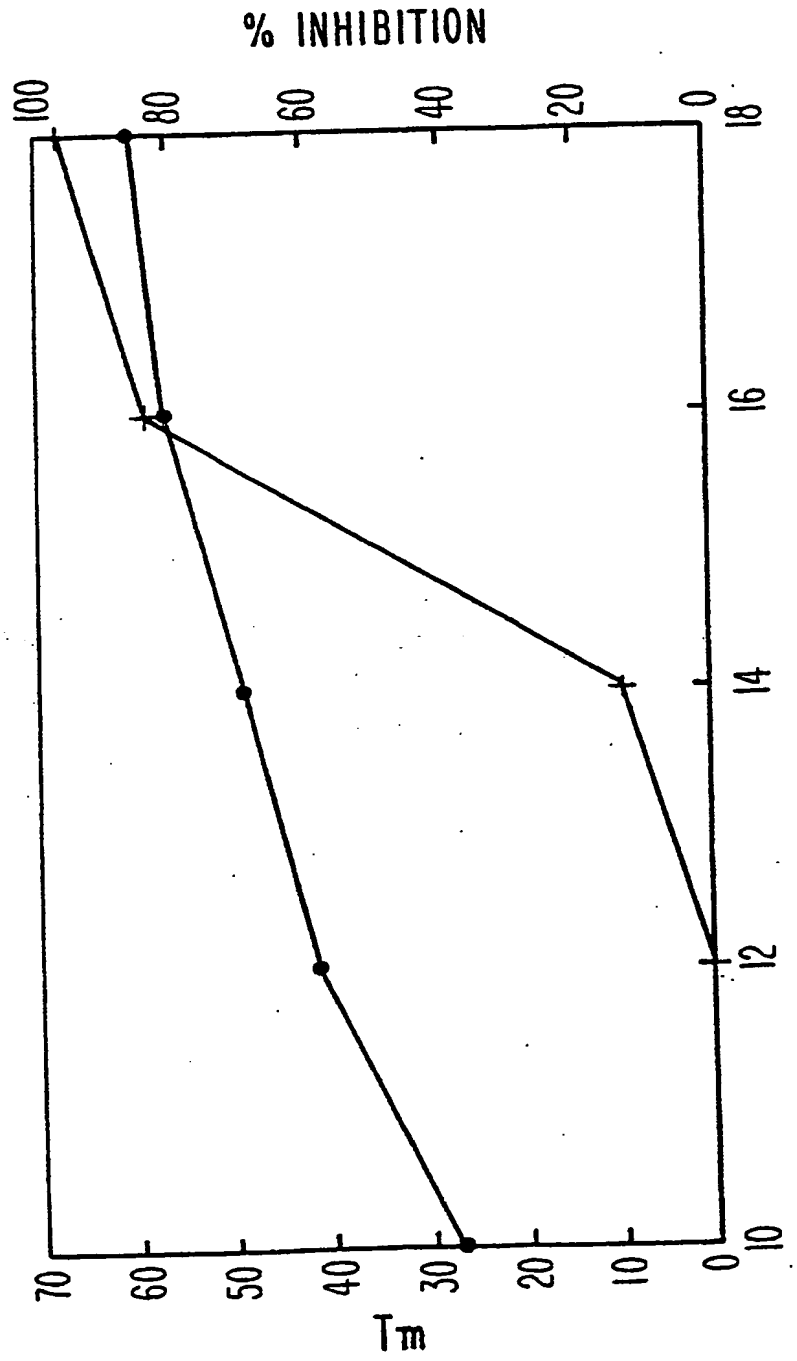
% INHIBITION
100
80
60
40
20
0
18
16
14
12
10
CHAIN LENGTH
70
60
50
40
30
20
10
0
Tm
• Tm + % INHIBITION
100 nM OLIGONUCLEOTIDE

FIG. 10

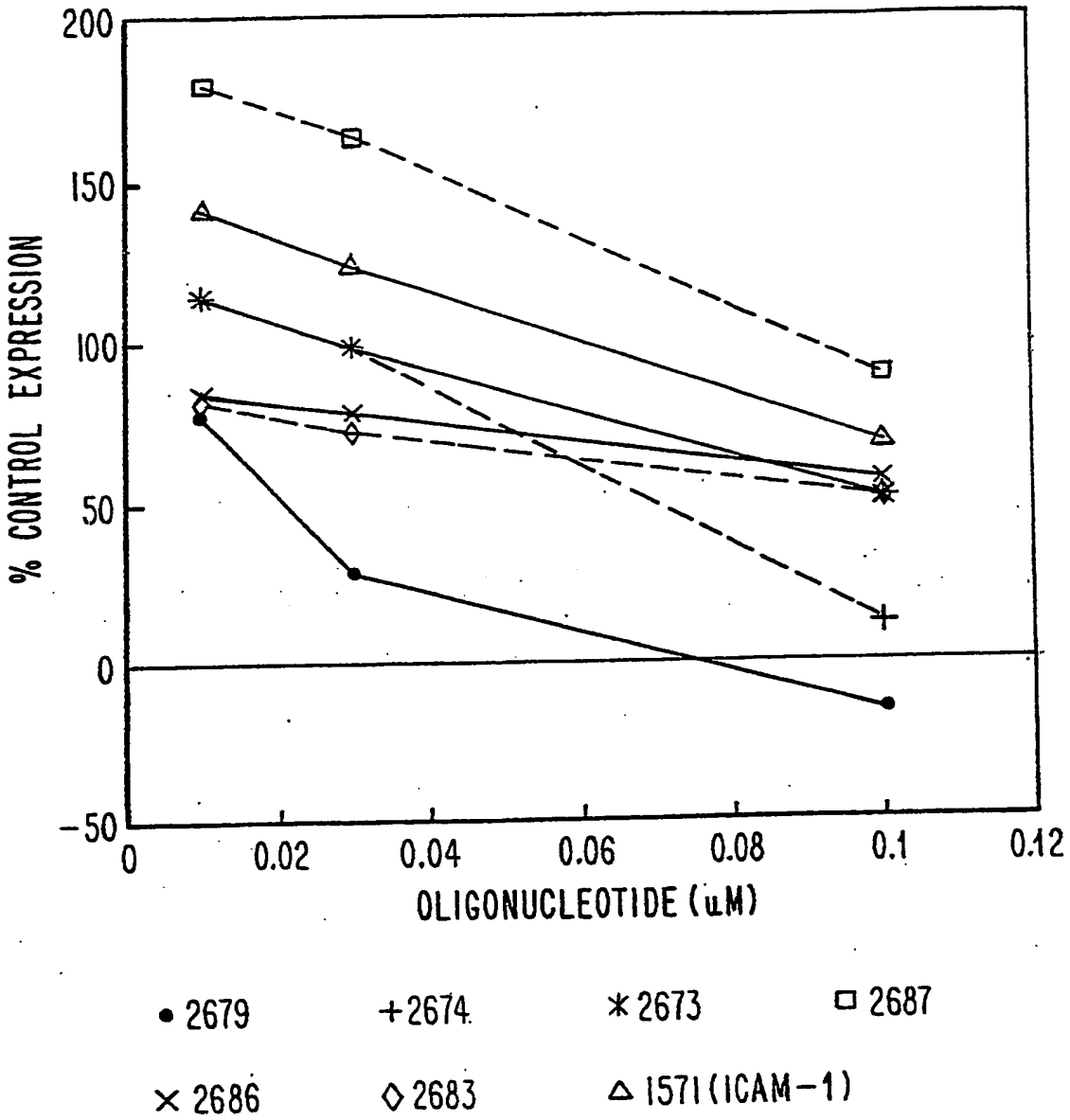
200
150
100
50
0
-50
% CONTROL EXPRESSION
0
0.02
0.04
0.06
0.08
0.1
0.12
OLIGONUCLEOTIDE (uM)
• 2679
+ 2674
* 2673
□ 2687
× 2686
◇ 2683
△ 1571 (ICAM-1)

FIG. 12

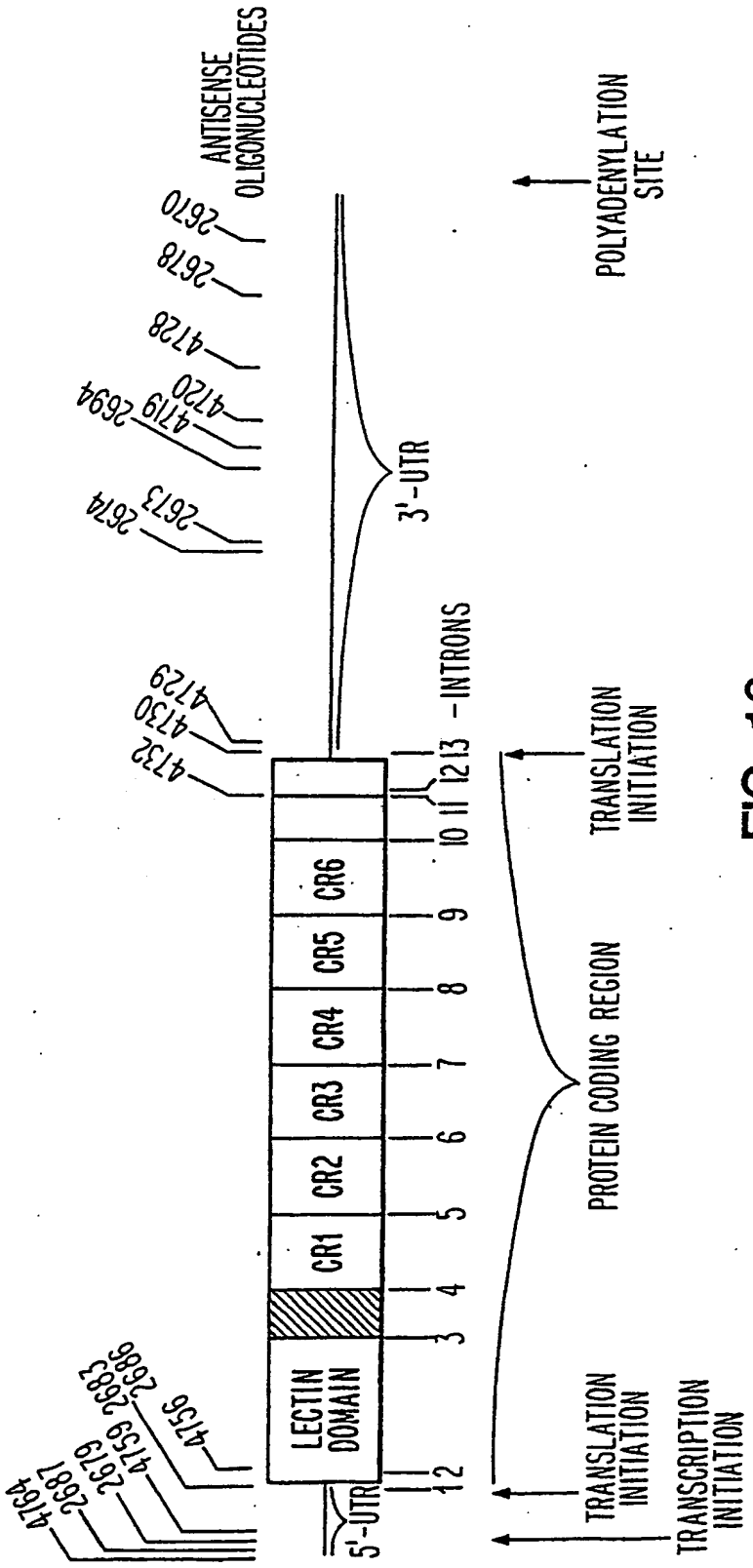
ANTISENSE OLIGONUCLEOTIDES
2670
2678
4728
4720
4719
2694
2673
2674
POLYADENYLATION SITE
3'-UTR
4729
4730
4732
-INTRONS
1 2 3 10 11 12 13
CR6
CR5
CR4
CR3
CR2
CR1
LECTIN DOMAIN
TRANSLATION INITIATION
PROTEIN CODING REGION
TRANSLATION INITIATION
TRANSCRIPTION INITIATION
5'-UTR
4756
2683
2686
4759
2679
2681
4764

FIG. 13

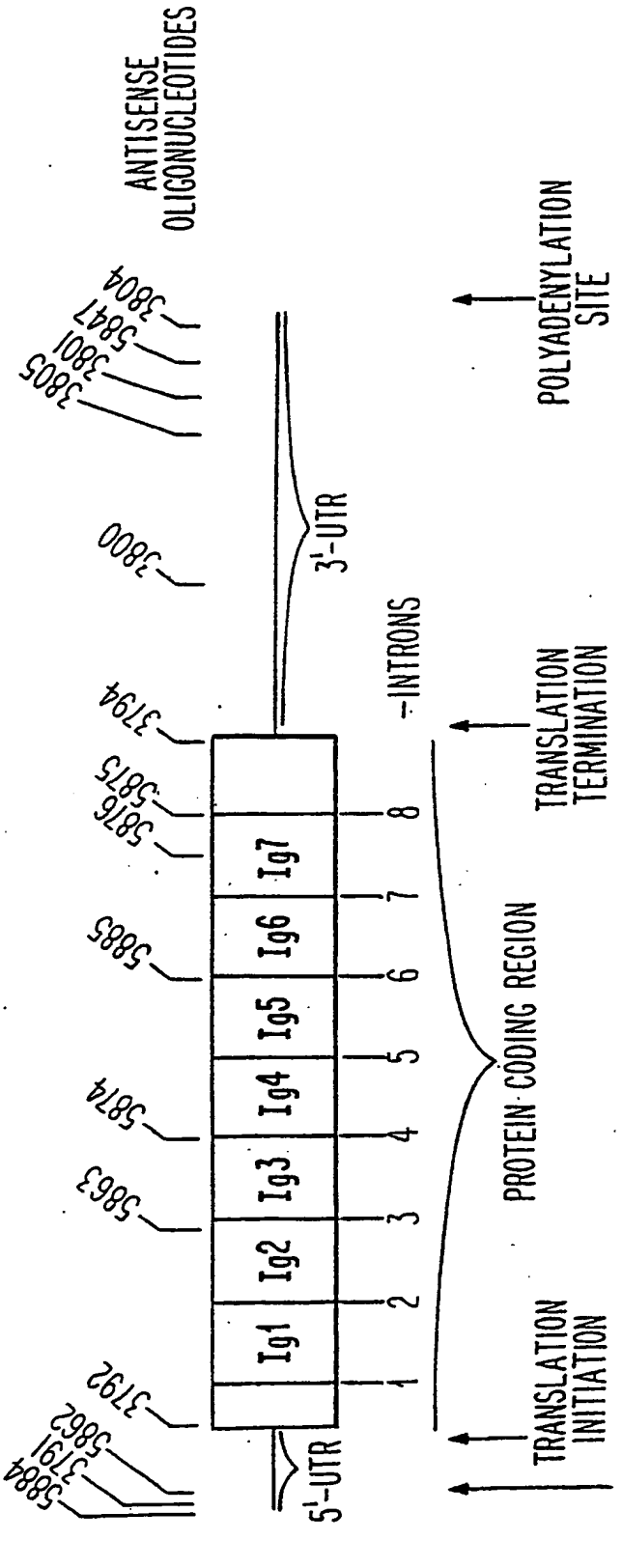
ANTISENSE OLIGONUCLEOTIDES
3804
3847
3801
3805
3800
3794
3792
3791
3862
3884
5876
5875
5885
5874
5863
5884
Ig1
Ig2
Ig3
Ig4
Ig5
Ig6
Ig7
1
2
3
4
5
6
7
8
5'-UTR
3'-UTR
-INTRONS
PROTEIN CODING REGION
POLYADENYLATION SITE
TRANSLATION TERMINATION
TRANSLATION INITIATION
TRANSCRIPTION INITIATION

FIG. 14

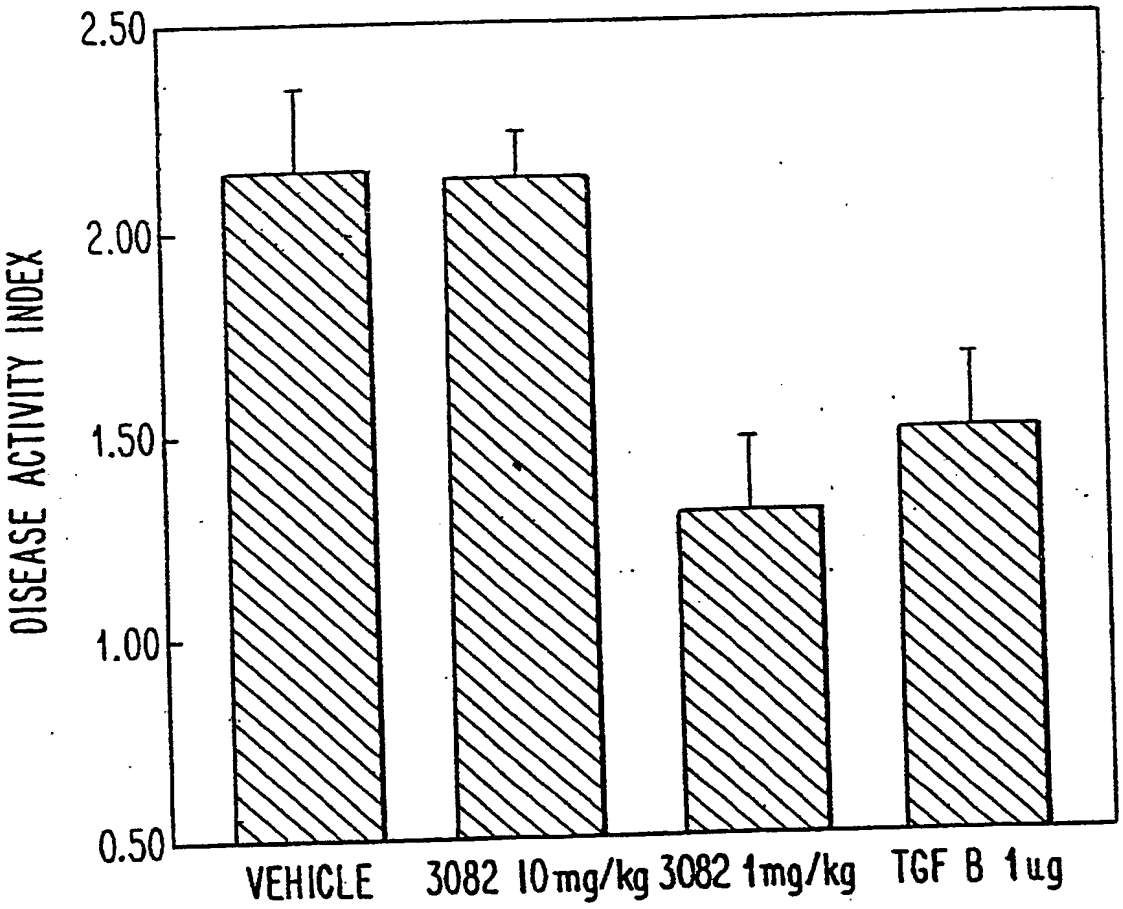
2.50
2.00
1.50
1.00
0.50
DISEASE ACTIVITY INDEX
VEHICLE
3082 10mg/kg
3082 1mg/kg
TGF B 1ug

FIG. 16

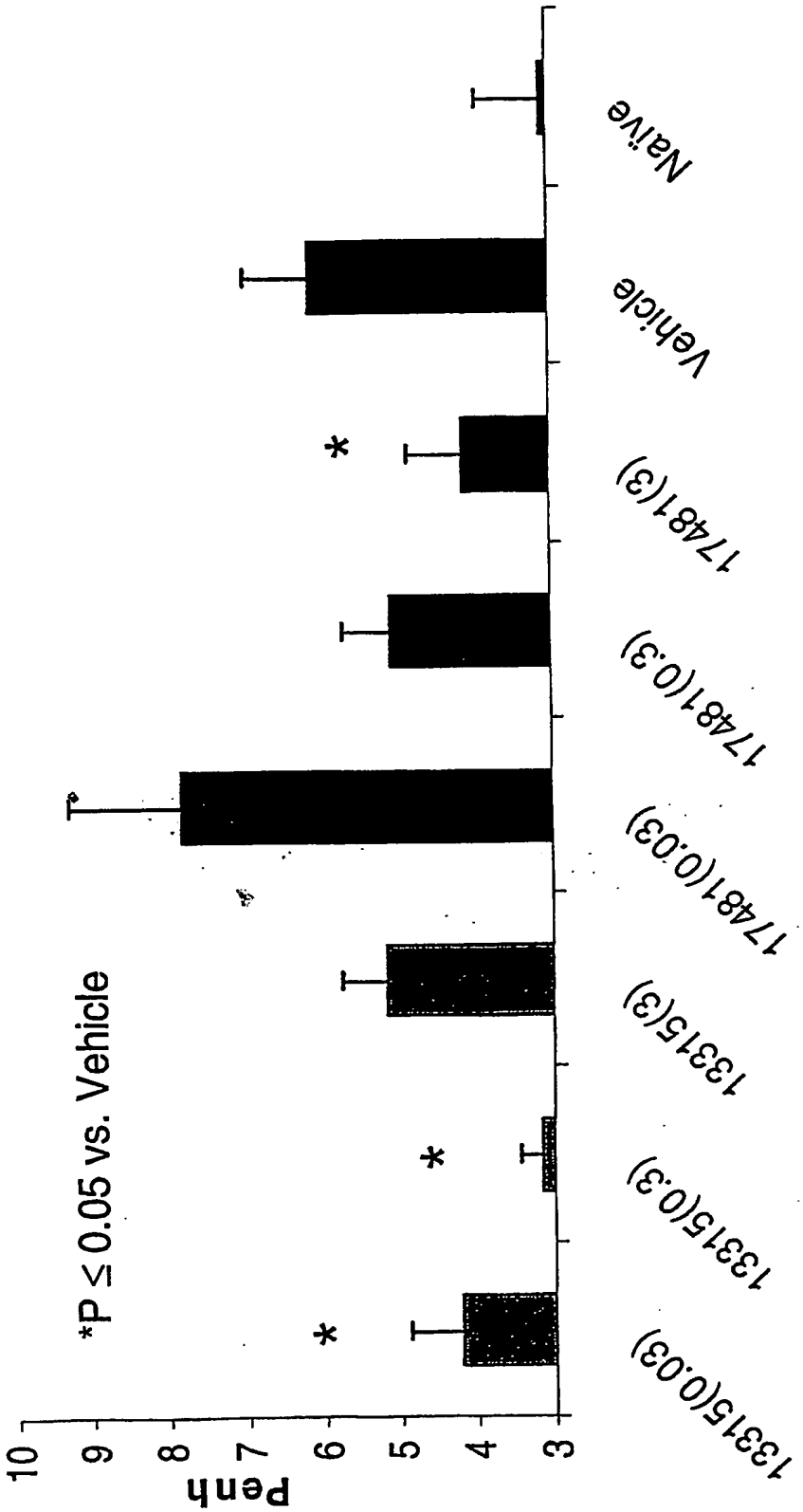
Naïve
Vehicle
1748I(3)
1748I(0.3)
1748I(0.03)
1331S(3)
1331S(0.3)
1331S(0.03)
*P ≤ 0.05 vs. Vehicle
Penh
10
9
8
7
6
5
4
3
*
*
*

FIG. 17

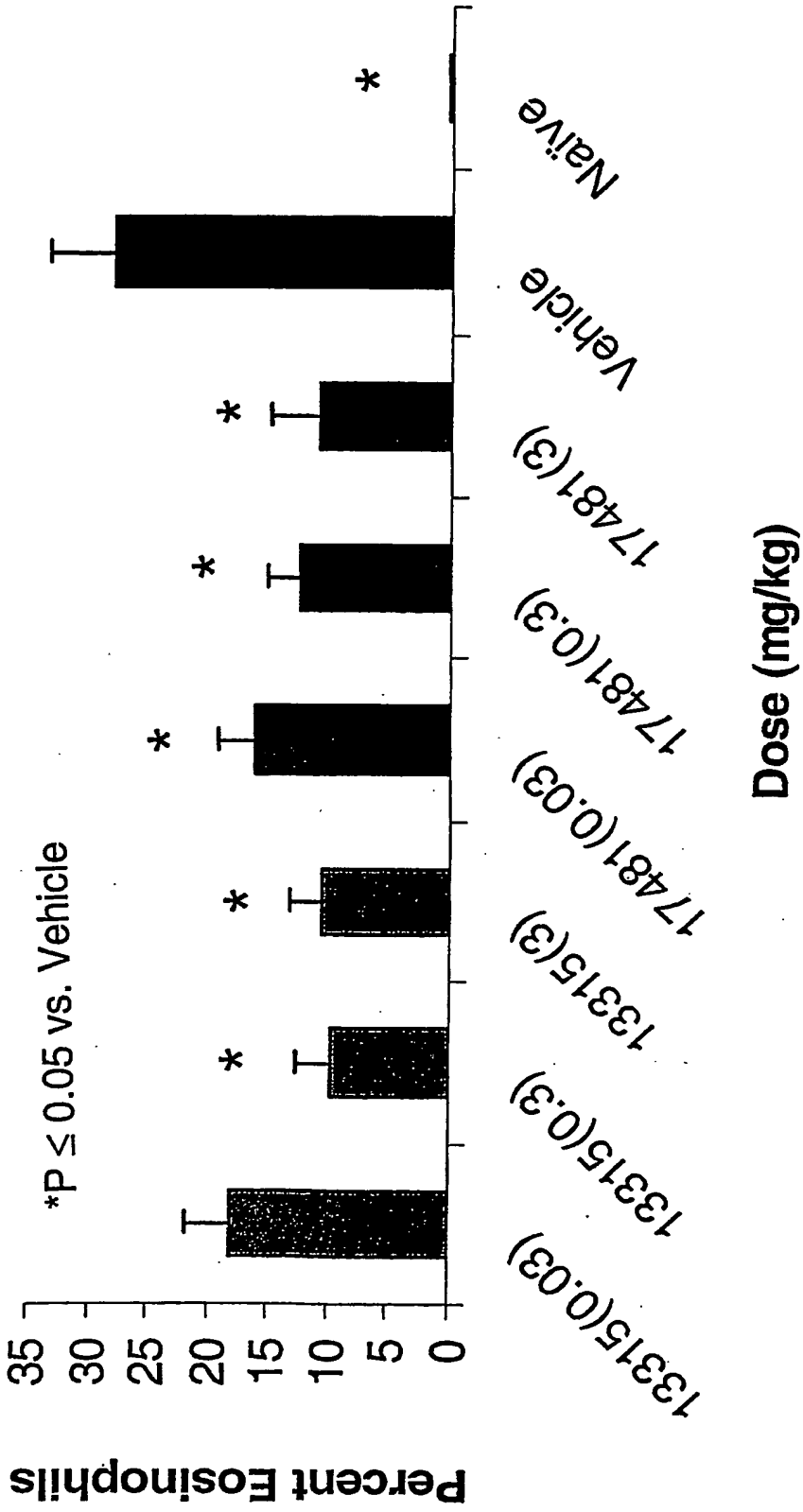
Percent Eosinophils
35
30
25
20
15
10
5
0
*P ≤ 0.05 vs. Vehicle
Dose (mg/kg)
1331S(0.03)
1331S(0.3)
1331S(3)
1748I(0.03)
1748I(0.3)
1748I(3)
Vehicle
Naïve

FIG. 18

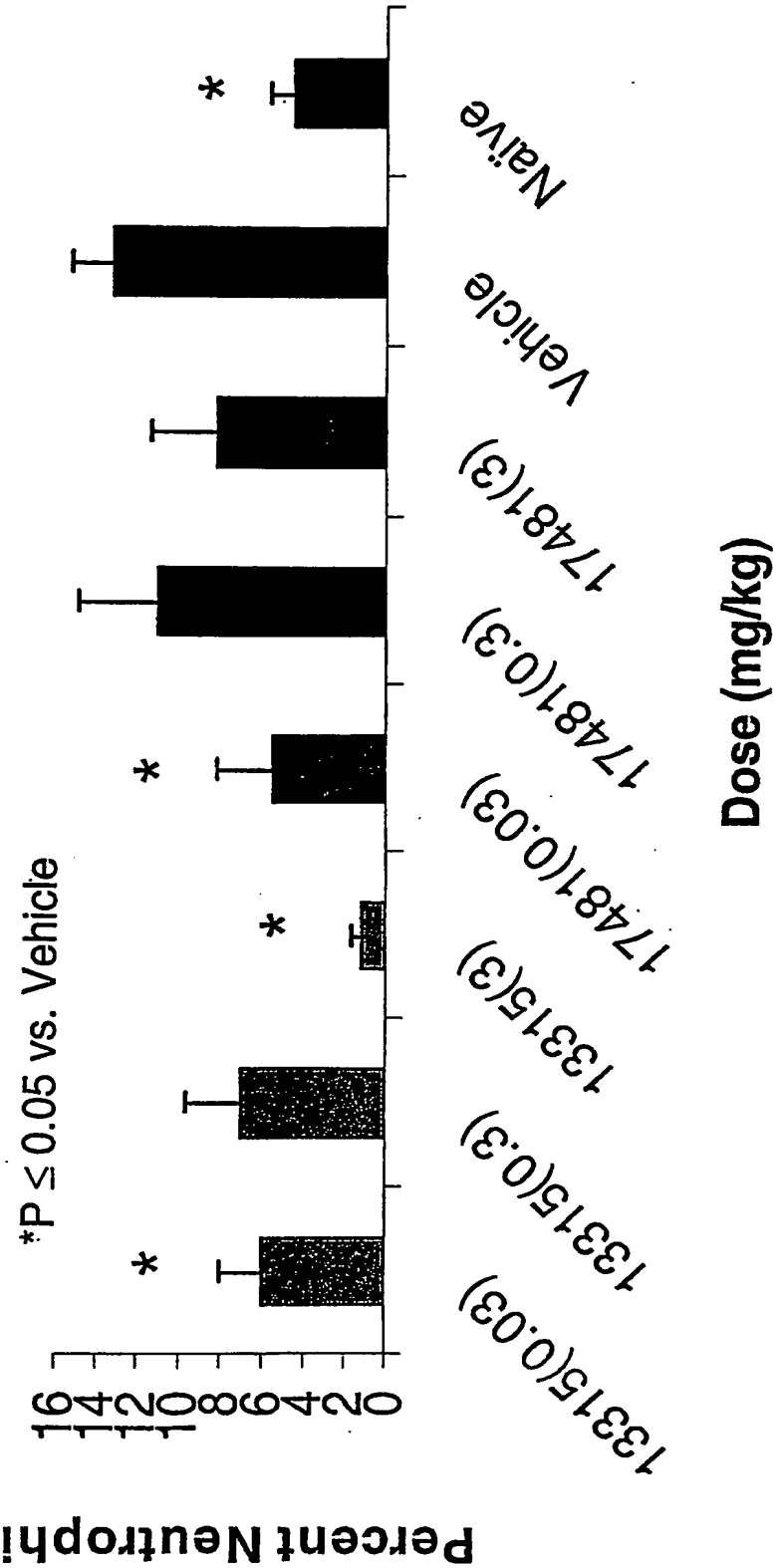
Percent Neutrophils
0
2
4
6
8
10
12
14
16
*P ≤ 0.05 vs. Vehicle
Dose (mg/kg)
1331.5(0.03)
1331.5(0.3)
1331.5(3)
1748.1(0.03)
1748.1(0.3)
1748.1(3)
Vehicle
Naïve

FIG. 19

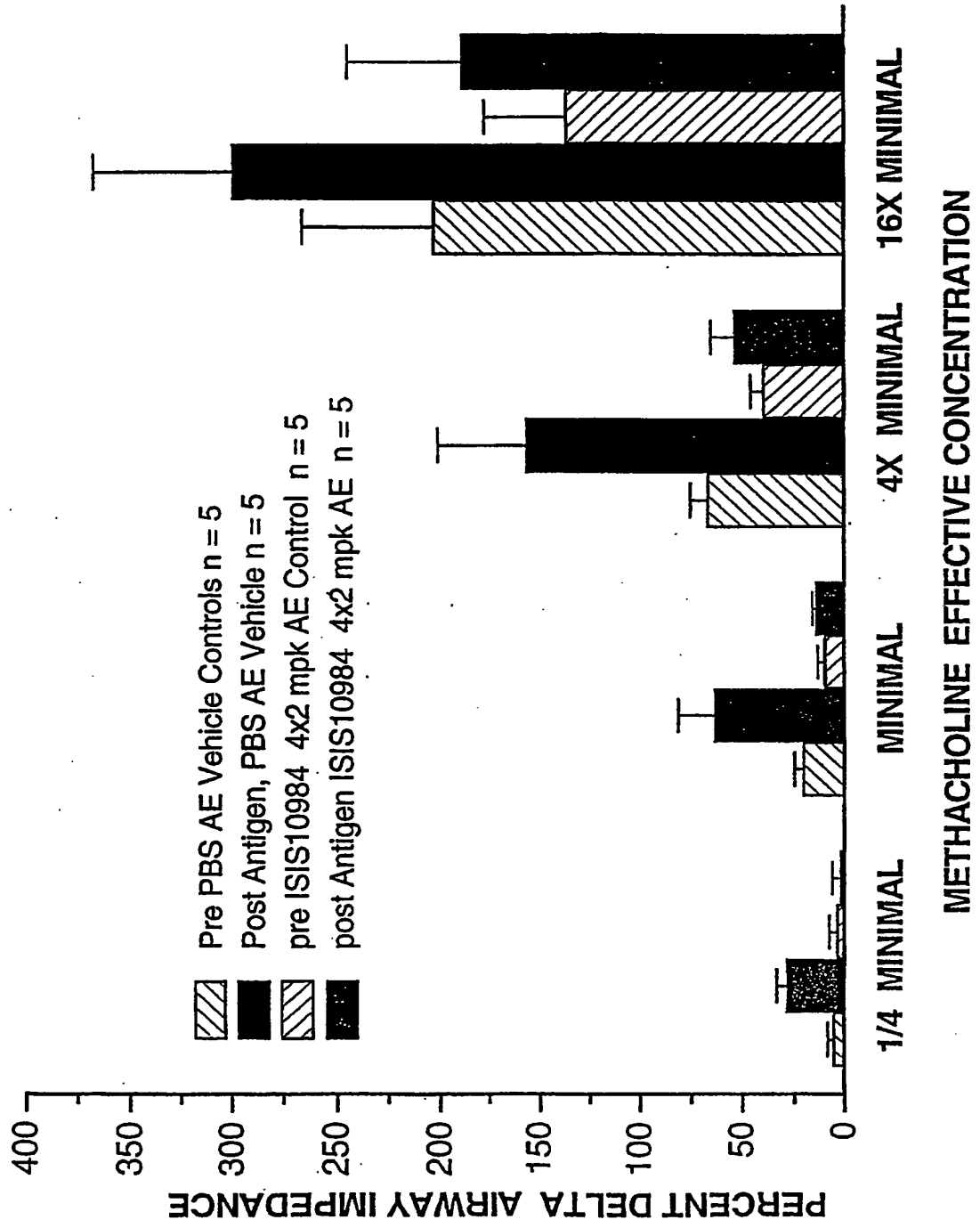
PERCENT DELTA AIRWAY IMPEDANCE
400
350
300
250
200
150
100
50
0
Pre PBS AE Vehicle Controls n = 5
Post Antigen, PBS AE Vehicle n = 5
pre ISIS10984 4x2 mpk AE Control n = 5
post Antigen ISIS10984 4x2 mpk AE n = 5
1/4 MINIMAL
MINIMAL
4X MINIMAL
16X MINIMAL
METHACHOLINE EFFECTIVE CONCENTRATION

Fig. 20